Probiotic vs. Placebo in Irritable Bowel Syndrome: A Randomized Controlled Trial

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ABSTRACT

BACKGROUND

This study assesses the potential effect of *Lactobacillus reuteri* as a single strain probiotic preparation (Biogaia®) on irritable bowel syndrome (IBS).

METHODS

Patients diagnosed with IBS who fulfilled Rome III criteria and consented to participate in this study were randomized to receive either the probiotic or an identical placebo once daily for four weeks. Patients used a questionnaire to record any symptoms and adverse reactions over a one-week run-in period and during the final two weeks of intervention. For each group, we calculated the differences between mean scores of the variables and compared the results between groups.

RESULTS

Frequency of defecation increased in the Biogaia® group and decreased in the placebo group meaningfully. But There were no significant difference in the two groups in other terms of bloating, sense of urgency for defecation, abdominal pain, stool shape, quality of defecation, sense of incomplete evacuation, and treatment satisfaction.

CONCLUSION

The frequency of defecation increased in the Biogaia® group and decreased in the placebo group, however this study did not classify patients according to diarrhea or constipated subgroups, the efficacy of this drug is not clear. Hence *Lactobacillus reuteri* was not better than placebo in controlling IBS symptoms in this study. However, considering the significant placebo effect in IBS patients, it may be necessary to conduct studies with larger numbers of participants to better assess the possible beneficial effects of Biogaia.

KEYWORDS
Irritable Bowel Syndrome; Probiotic; *Lactobacillus Reuteri*

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INTRODUCTION

Irritable bowel syndrome (IBS), a common complaint observed in clinical practice, is characterized by abdominal pain, feeling of excessive gas and altered bowel habit in the absence of any structural, inflammatory or biochemical abnormalities.[1] IBS affects approximately 15% of the general population and has a female predominance. It is also observed in children.[2]

IBS is a chronic, recurring disease, which although not fatal, it affects the quality of patients' lives by mandating frequent medical attention and increased job absences. Therefore, in most cases, some form of treatment should be offered to patients.

The pathogenesis of IBS is not well understood. Etiologies that include altered gastrointestinal motility, visceral hyperalgesia, stress, altered intraluminal microflora and immune system activation have been proposed.[3] Intestinal microbiota are important against carcinogens, for vitamin production and bile acid degradation, in addition to barriers against pathogens. Additionally, intestinal microbiota have a pivotal role in immune system development and function.

The increased risk of IBS after gastroenteritis is well recognized and suggests a possible role of change in microflora and activation of the immune pathways in its pathogenesis.[4] Significant reduction in Lactobacillus and Bifidobacterium levels in IBS patients have been reported.[5]

Current medications for IBS are generally unsatisfactory. Considering the recent knowledge regarding gut flora and its alteration in IBS patients, manipulating the microbiota has been proposed as a plausible way to control IBS.[6] Probiotics are live organisms such as Lactobacilli and Bifidobacteria which are believed to be of benefit to the health of the host when ingested in adequate amounts.[7] There are several studies on the effects of probiotics in IBS patients with variable and conflicting results. In this study we have assessed the effects of *Lactobacillus reuteri* (Biogaia ®) in a single blind, randomized, placebo-controlled clinical trial on symptom relief in IBS patients.

MATERIALS AND METHODS

This was a randomized parallel group, single blind, placebo-controlled study. According to a previous study, the mean change in symptom score was 3.12 for Biogaia® and 1.98 for the placebo group, with a SD of 2.46. Hence, for the current study we calculated the sample size as 36 participants per study group with an 80% statistical power at a 5% level of significance.[8]

Consenting patients who fulfilled Rome III criteria for IBS and referred to two outpatient gastroenterology referral clinics in Tehran, Iran were consecutively enrolled. Those who declined to participate received routine care. The study was approved by the Ethics Committee of the Digestive Disease Research Institute, Tehran University of Medical Sciences in accordance with the 1975 Declaration of Helsinki.

All patients were required to have normal CBC, FBS, ESR, CRP and liver function tests, in addition to normal serum creatinine, thyroid function, anti-endomysial antibody, urinalysis and stool for occult blood and ova/parasites prior to beginning the study.

Exclusion criteria were: pregnancy, breast feeding, diabetes mellitus, uncontrolled thyroid disease, prior abdominal surgery other than appendectomy, cholecystectomy, cesarean section, herniorrhaphy, hysterectomy, tubal ligation, immune deficiency, chronic renal disease and chronic liver disease. Patients were also excluded if they used any of the following medications within 14 days prior to study entry: antispasmodics, laxatives, antidiarrheal, probiotics, symbiotics, narcotics or antibiotics.

Patients were randomized to receive either the study drug (Biogaia®) or an identical placebo (one tablet qd) for four weeks. The medication was provided to the patients at their baseline visit. The study drug contained 100 million live *Lactobacillus reuteri*. Patients were randomized via a simple randomization process using a computer generated random table. At baseline, a questionnaire was used to assess patients' IBS symptoms that included abdominal pain, bloating, sense of urgency for defe-

cation, frequency of defecation, stool shape, quality of defecation and sense of incomplete evacuation. Patients completed the same questionnaire every other day for one week, and refer then to receive the medication. We gave the same questionnaire to the patients at the time they received the medication. Patients were instructed to complete this questionnaire twice weekly for the last two weeks of taking the medication. Patients were requested to record the onset of any new symptoms during the study period as well as their overall satisfaction with the study treatment.

Continuous variables were presented as mean ± standard deviation (SD). We analyzed symptoms by repeated measures analysis. The group was considered as a between-subjects factor and all analyses were adjusted for age as the covariate. We used the chi-square test to evaluate the association of the categorical variables. Two-sided $p<0.05$ was considered statistically significant. SPSS 19.0 (Chicago, Illinois) was used for all statistical analyses.

RESULTS

A total of 120 consecutively consenting patients were enrolled (n=60 per group). We excluded 7 patients from the probiotic group due to a protocol violation (concomitant use of laxatives) and/or invalid data recording. One patient in the placebo group was excluded after it was determined that she was pregnant. A total of 20 patients withdrew from the study. Final analyses were performed on 92 patients. There were 15 (38.5%) males in the placebo group and 21 (39.6%) in the probiotic group (p=0.91). Patients' mean age in the placebo group was 37.7 ± 10.5 years versus 44.9 ± 13.0 years for the probiotic group (p=0.005).

Table 1 shows the scores for different symptoms assessed before and after treatment in both groups. As seen in Table 2, adverse events were similar between groups.

DISCUSSION

In the present study, we observed no statistically significant differences between the probiotic and placebo groups. The mean scores for frequency of defecation increased in the Biogaia® group and decreased in placebo group after treatment. We did not take into consideration the diarrhea or constipation predominant subgroups, hence it was not clear if patients benefited from Biogaia® in the probiotic group. According to several systematic reviews and meta-analyses of probiotics in IBS, there is a consensus of opinion regarding the beneficial effects of probiotics in the reduction of IBS symptoms as a whole. In a small study of 55 IBS patients who have received *Lactobacillus reuteri* treatment for six months, the researchers observed improvements in patients' global symptoms compared to baseline however this treatment was not superior to placebo because of the high placebo effect. That study had a longer treatment period compared to the current study, which might be the explanation for the difference in results. Another small study of 40 patients with IBS showed that treatment with *L. acidophilus* for four weeks was superior to placebo in decreasing abdominal pain.[9] A randomized controlled trial of a combination of probiotics (VSL3) and placebo showed significant decrease in flatulence.[10] Nevertheless, variable results exist in different studies which have been unable to show a significant response to probiotic therapy.[11] Two double-blind, placebo controlled studies did not show the effectiveness of probiotics on IBS symptoms. *Lactobacillus plantarum* and *Lactobacillus casei* did not improve symptoms.[12,13]

Our data did not show any difference between *Lactobacillus reuteri* and placebo in improving IBS symptoms. This might be due to the small number of enrolled patients, relatively short duration of therapy, microbiota strain used and its dose. The small sample size was the limitation of this study. Study patients are continuing with follow up visits, for which we will assess the results. Further studies that enroll larger numbers of participants for a longer duration of treatment may help with further clarification of the benefits of various probiotics, including the one used in this study, for the management of IBS symptoms.

In this study we have shown that *Lactobacil-*

Table 1: Summary of repeated measures analysis.

Symptoms (mean±SD)	Probiotic (Biogaia®) N=41			PlaceboN=31			*p*-value for interaction
	Before	After	*p*-value	Before	After	*p*-value	
Abdominal Pain Score	2.09±1.66	1.57±1.71	0.650	1.67±1.62	1.11±1.26	0.739	0.311
Bloating Score	2.69±1.76	2.25±1.65	0.852	2.32±1.78	1.78±1.41	0.579	0.657
Urgency Score	1.75±1.77	1.32±1.72	0.285	1.52±1.34	1.26±1.27	0.966	0.859
Frequency Number	1.48±1.51	1.54±1.18	0.048	1.90±1.45	1.83±1.28	0.050	0.091
Evacuation Score	0.93±0.27	0.92±0.26	0.382	0.97±0.18	0.92±0.26	0.854	0.940

All analyses were adjusted for age.

Table 2: Adverse events (AE) reported by study participants.

Adverse events (AE)	Probiotic (Biogaia®) N(%)	Placebo N(%)	*p* -value
Diarrhea	2 (4.9)	0	0.503
Bad oral taste	1 (2.4)	0	1.00
Epigastric fullness	1 (2.4)	0	1.00
Anal pain	1 (2.4)	0	1.00
Dark green stool	1 (2.4)	0	1.00
Dry lips	0	1 (3.2)	0.431
Headaches	1 (2.4)	0	1.00
Hiccups	0	1 (3.2)	0.431
Belching	2 (4.9)	1 (3.2)	1.00
Puffiness	0	1 (3.2)	0.431
Palpebral pruritus	0	1 (3.2)	0.431
Skin rash	1 (2.4)	1 (3.2)	1.00
Epigastric burning	1 (2.4)	0	1.00
Heartburn	2 (4.9)	1 (3.2)	1.00
Nausea	1 (2.4)	1 (3.2)	1.00
Bloating	6 (14.6)	0	0.033
Abdominal pain	3 (7.3)	3 (9.7)	1.00
Constipation	6 (14.6)	0	0.033
At least one AE	14 (34.1)	8 (25.8)	0.447

The most frequent adverse events observed were bloating and constipation in both groups.

lus reuteri (Biogaia®) is not better than placebo in controlling IBS symptoms. However, additional research with subgroups of patients that have diarrhea or constipation symptoms are needed to more efficiently assess the resultant data. The current study has assessed global symptoms. In order to evaluate our findings we should conduct a more organized study that includes a more specific questionnaire. In addition, by taking into consideration the significant placebo effect in IBS patients, studies with larger sample sizes may better assess the beneficial effects however it is necessary to further study the formulation and bioavailability of Biogaia®.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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